REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-3, 5, 6, 12-29 are pending in this application. Although claims 6, 28 and 29 have been withdrawn from consideration on the Office Action Summary form, claims 28 and 29 are cited as being examined in several locations in the actual body of the office action such that its inclusion cannot be attributed to a typographical error (page 2, page 4 and page 6). As such, the applicants presume for the purposes of this response that claims 28 and 29 have also been examined. No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112.

Third Request for removal of 3rd party document from Image File Wrapper

Upon review of the Image File Wrapper (IFW) for this application, in addition to the papers associated with the Office Action which were entered into the IFW on 7 February 2008, there was also a file described as "Claims" which was also entered on this date.

The applicants did not submit this file and the claims in this document appear to be directed to another application (SN: 11/680,727 – "X-Ray Recording Device with an X-Ray Detector and an X-Ray Emitter") which is not owned by the applicants or is being prosecuted by the applicants' representatives. There was no indication in the Office Action that this was intended to be part of the papers to be mailed to the applicants.

As this paper appears to be unrelated to the present invention and was inadvertently entered by the PTO, the applicants again request removal of this file from the IFW for this application (Upon further review, this paper appears to be associated with a different application being examined by the same Examiner of record in this application).

II. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

Note: As there has been no indication that the restriction/election of species has been withdrawn or that the scope of the examination was expanded beyond the applicants' elected species, the invention was presumed to be examined for the election wherein:

1. The patch is a matrix-type patch
2. The adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer
3. The another penetration enhancer is an N-methyl pyrrolidone
4. The preservative is an organic acid
5. The backing comprises of polyester.

As such, by virtue of the restriction/election of species requirement, this election was deemed to be patentably distinct from other elections which could have been made by the applicants.

Claims 1-3, 5, 12-14, 28 and 29 were rejected as allegedly being obvious over Kleinsorgen et al. (U.S. Patent 6,165,499 - Kleinsorgen).

In order to establish *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art reference or be within the knowledge of those of ordinary skill in the art. *See MPEP 2143.03.* In addition, because of the restriction requirement, any reference which fails to teach any of the elected elements described above, would be considered to be a patentably distinct invention. *See MPEP 806.04(h).* As such, Kleinsorgen fails to teach or suggest all of the limitations of the applicants' transdermal formulations.

1. Evidence of secondary considerations

Although a new grounds of rejection was made over Kleinsorgen which rendered the previous rejection moot, this does not absolve the responsibility of considering evidence of secondary considerations when making a determination of obviousness. No comment was made about the arguments and data provided in the applicants previous response and as such for this reason alone, the applicants' claimed invention in unobvious over Kleinsorgen. The applicants previous response on this matter is reproduced below:

When considering the applicants invention as a whole, the present invention provides a solution for the problem of imparting a pharmaceutical formulation with properties which enable an opiod analgesic to be transdermally administered. The solution for this problem consists in

- a transdermal formulation comprising
- a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer,
- an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and
- an aloe composition as transdermal penetration agent.

With respect to amended claim 1, the formulation comprises a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer.

The inventors have carried out comparative experiments which are similar to Example 1 in the specification and which are now presented for the first time with this submission in the Declaration by Dr. Elisabeth Meyer.

In Example 1 of the description of the present application experiments with different matrix patches are presented. The results are summarized in Table I on page 16 of the description. A matrix patch is provided which comprises a mixture of buprenorphine (the analgesic), an aloe (the transdermal penetration agent) and a styrene-butadiene-styrene polymer (the adhesive). Flux experiments with hairless mouse skin reveal buprenorphine fluxes in the range from 0.8 to 2.3 $\mu g/cm^2*h$ and the transdermal penetration effect of aloe compositions.

In the comparative experiments the styrene-butadiene-styrene polymer (the adhesive) was replaced by several acrylate adhesives, i.e. the adhesive which is disclosed by Fischer as the usual adhesive in combination with the intradermal penetration agent (the aloe composition) and the drug.

The results as disclosed in the description and the results of the comparative experiments are presented in the following table below (see next page):

Adhesive type	PSA	Buprenorphine (% w/w)	*Aloe vera* (% w/w)	Flux (hairless mouse skin)	**Formation of crystals**
Examples of the Present Invention (cf. Table I of the invention, page 16)					
Styrene-butadiene-styrene polymer	DT 6173	15	20	2.3 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	5	20	0.8 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	10	10	0.9 µg/(cm^2*h)	–
Comparative Examples					
Acrylate-vinylacetate with carboxy groups	DT 2825	10	10	1.1 µg/(cm^2*h)	+
Acrylate-vinylacetate with hydroxyl groups	DT 2287	10	10	1.1 µg/(cm^2*h)	+
Acrylate with functional hydroxy groups	DT 2510	10	10	1.3 µg/(cm^2*h)	+
Acrylate-vinylacetate without functional groups	DT 4098	10	10	1.5 µg/(cm^2*h)	+

It should first be noted that in the description of the present application the fluxes are accidentally given as g/(cm^2*h). In fact, also in the case of the invention the fluxes are in the micro gram range and should read as µg/(cm^2*h) which is corrected in the specification.

When comparing the results of the above experiments in which the patches comprise 10 % (w/w) *Aloe vera* it turns out that the fluxes which are obtained with the styrene-butadiene-styrene polymers as adhesive (according to the invention) and with the acrylates as adhesives (comparative examples) are similar. ***However, with the acrylate polymers a disadvantageous crystallization of the drug (buprenorphine) in the matrix is observed over the time.*** Such a crystallization reduces the long term stability of the formulations and the amount of drug available for the transdermal penetration is very disadvantageous for transdermal applications, for which a relatively high concentration of the dissolved drug in the pharmaceutical formulation is needed. This disadvantageous crystallization effect can be avoided using the styrene-butadiene-styrene polymers of the invention.

2. Kleinsorgen is not directed toward a combination of an opioid analgesic and an aloe composition

In addition to the elements elected from the restriction requirement, the applicants' claimed invention also requires the combination of an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient ("opioid analgesic") and an aloe composition as transdermal penetration agent.

When considering the Kleinsorgen reference as a whole, it is clear that Kleinsorgen is directed toward the therapeutic system itself, i.e. a system comprising a substrate (1) provided with a separating layer (2), a film layer (3) comprising the active substance, and a protective layer (4) provided with a non-stick finish, the separating layer (2) consisting of a material whose bond to the film layer (3) may be abolished, i.e. the solution to the problem lies in the elements of Kleinsorgen's system not the active ingredients which can be part of the system. *See* Abstract.

There is no teaching or direction for the specific combination of opioid analgesic and aloe composition from with Kleinsorgen as the reference makes broad recitations to "transdermally applicable active substances" (see col. 5, line 44 – col. 6, line 17). This alone would not render the applicants claim to be obvious over Kleinsorgen as this does not represent a finite number of solutions to the problem to be solved and as noted earlier, selection of the appropriate active substance is not even the problem Kleinsorgen is trying to solve.

When considering that one of ordinary skill in the art must also select an aloe composition in combination with the opioid analgesic, the logic for obviousness is even more remote especially given the fact that within Kleinsorgen, aloe vera is merely one of many possible vegetable preparation which can be used and the fact that the use of a vegetable preparation is an optional element within the teaching of Kleinsorgen (see col. 6, lines 18-49).

Moreover, MPEP 2144.04 states that "...if the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." However, the case law citations on page 5 of the Office Action regarding the obviousness of combining multiple compounds are not appropriate for the facts in the present application.

In the interest of brevity, the applicants address a representative citation, i.e. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)("It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose.")

To summarize *Kerkhoven*, the court found that it would have been obvious to combine a known detergent composition with another known detergent composition and to have expected a third detergent composition. However, this is not the factual basis for the current rejection.

The opioid analgesic is being used for its art recognized effect as an analgesic and aloe vera is being used as a transdermal penetration agent. While the reasoning for combining two compounds does not have to be the same as the applicants' reasons, in the present case, neither one of ordinary skill in the art (nor a judge) would find that Kleinsorgen was using aloe vera as an analgesic even presuming there was any direction for selecting an opioid analgesic as the active ingredient.

As such, there is no basis for the assertion that the combination of an opioid analgesic with an aloe composition would have been obvious from Kleingsorgen.

3. Detemination of obviousness must also consider the effect of the restriction requirement and dependent claims

As the restriction requirement is still in force, the application under examination is for a formulation which must have the elements that the (1) patch is a matrix-type patch; (2) the adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer; (3) the another penetration enhancer is an N-methyl pyrrolidone; (4) the preservative is an organic acid; and (5) the backing comprises of polyester.

In addition to the deficiencies of Kleinsorgen mentioned above, there is nothing which suggests that Kleinsorgen has a transdermal system which simultaneously has all five of these elements. Furthermore, the restriction requirement is prima facie evidence than any element missing from these five elected elements constitutes a patentably distinct invention.

Lastly, claim 12 is directed toward a specific opioid analgesic, i.e. buprenorphine, the specificity of which is even less obvious given the virtually infinite number of potential compounds which could be used as an active agent within Kleinsorgen.

4. Conclusion

Any of the above reasons alone establish that Kleinsorgen does not render the applicants' claimed invention to be obvious and when considered collectively, Kleinsorgen is far removed from establishing a *prima facie* case of obviousness and therefore, this rejection may be withdrawn.

Claims 1-3, 5 and 12-29 were rejected as allegedly being obvious over Kleinsorgen et al. (U.S. Patent 6,165,499 - Kleinsorgen) as applied to claims 1-3, 5, 12-14, 28 and 29 in view of Fischer et al. (U.S. Patent 6455066 – "Fischer")

Fischer is being relied upon in combination with Kleinsorgen presumably to address claims 15-27. As claims 15-27 are either directly or indirectly dependent upon claims 1-3, 5, 12-14, 28 and 29 which the applicants have established is not obvious in view of Kleinsorgen, claims 15-27 are also unobvious in light of Kleinsorgen and Fischer. However, the applicants provide further comments as to why the combination of Kleinsorgen and Fischer does not render claims 15-27 obvious.

As earlier noted, the applicants' invention is directed toward a ***transdermal*** formulation whereas the invention of Fischer is directed toward an ***intradermal*** composition. The differences in administration is well known in the art and is even addressed by Fischer themselves in the background of their invention (see col. 1, lines 39-48).[1] As one of ordinary skill in the art would recognize that intradermal administration is intended to ***avoid*** any transdermal absorption, the Fischer reference would not be readable upon or suggestive of the applicants' transdermal formulation nor would be recognizable by one of ordinary skill in the art to be relevant for combination with a reference which is directed to transdermal systems such as Kleinsorgen.

Second, Fischer is directed toward the delivery of an ***anesthetic*** whereas the applicants' transdermal formulation is directed toward delivery of an ***opioid analgesic*** from the phenanthrene group which is consistent with their disclosed methods of delivery, i.e. Fischer wants localized delivery of their anesthetic and to avoid systemic delivery whereas the applicants' invention wants to provide systemic delivery to maximize the pain relief associated with the opioid analgesic.

Moreover, Fischer recognized that the behavior of a penetration enhancer is strongly dependent on the drug (see col. 2, lines 35-41) and as such one of ordinary skill in the art would not impute the penetration activity of aloe vera with an anesthetic as being predictive of the

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[1] "In general, drug administration via the skin is divided into two categories: 1) ***transdermal*** administration and 2) ***intradermal*** administration. Transdermal administration involves transport through the skin and into the blood stream to treat systemic diseases. One the other hand, intradermal administration is intended to impart a cutaneous effect, while keeping the pharmocological effects of the drug localized to the intracutaneous regions of drug penetration and deposition. ***Ideally, intradermal absorption occurs with little or no systemic absorption or accumulation.***" (emphasis added)

activity with an opioid analgesic and in this instance, it is uncertain what relevance of such predictability would be as Fischer and the applicant are directed toward inventions with opposite modes of action.

Third, Fischer also lacks a teaching for some of the elected features of the applicants' claimed invention, i.e. Fischer does not teach a matrix-type patch or that the adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer.

The applicants further add that Fischer is silent as to the adhesive being comprised of styrene-butadiene-styrene block copolymer.

For these reasons, the combination of Kleinsorgen and Fischer does not render any of the applicants' pending claims to be obvious.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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